Amphotericin B

Brand Name: Amphocin, Fungizone, AmBisome, Abelecet, Amphotec

Drug Description

Amphotericin B is an amphoteric polyene macrolide antibiotic produced by Streptomyces nodosus. Amphotericin B formulated with sodium deoxycholate was the first parenteral amphotericin B preparation available commercially. Because amphotericin B deoxycholate is associated with certain dose-limiting toxicities (principally nephrotoxicity), other parenteral amphotericin B preparations have been developed with lipid-based drug delivery systems. Amphotericin B is now commercially available as amphotericin B cholestryl sulfate complex (Amphotec), amphotericin B lipid complex (Abelcet), and amphotericin B liposomal (AmBisome). [1]

HIV/AIDS-Related Uses

Amphotericin B deoxycholate is indicated in the treatment of invasive fungal infections, including aspergillosis, disseminated candidiasis, coccidioidomycosis, cryptococcosis, and histoplasmosis, which are common opportunistic infections in HIV infected patients. Due to concern about nephrotoxicity and the availability of alternative treatments (voriconazole, caspofungin, and lipid amphotericin formulations), the indication for amphotericin B deoxycholate therapy is limited to patients who have normal renal function, will receive less than 2 weeks of therapy, and have conditions that cannot be treated with azole antifungals.[2]

Amphotericin B deoxycholate is used as an alternative agent for long-term suppressive (i.e., secondary prophylaxis) or maintenance therapy to prevent recurrence or relapse of coccidioidomycosis, cryptococcosis, or histoplasmosis in HIV infected individuals who have received adequate treatment of the infection. Long-term suppressive or maintenance therapy is generally continued for life. The U.S. Public Health Service and Infectious Diseases Society of America make no recommendations for discontinuing therapy in patients receiving antiretroviral therapy who have CD4 cell counts above 100 cells/mm3. However, limited data suggest that discontinuing suppressive therapy in HIV infected adults and adolescents may be associated with low risk for recurrence of cryptococcosis. Individuals who consider discontinuing suppressive therapy should have successfully completed initial therapy for cryptococcosis, remained asymptomatic with respect to cryptococcosis, and have sustained (longer than 6 months) CD4 cell counts greater than 100 to 200 cells/mm3 in response to potent antiretroviral therapy.[3]

Non-HIV/AIDS-Related Uses

Amphotericin B is indicated in the treatment of a variety of invasive fungal infections, including aspergillosis, blastomycosis, disseminated candidiasis, coccidioidomycosis, cryptococcosis, histoplasmosis, mucormycosis, and sporotrichosis. It is indicated for treatment of fungal endocarditis, intra-abdominal infections, meningitis, septicemia, and urinary tract infections. Because of its toxicity, amphotericin B deoxycholate is indicated primarily in patients with progressive, potentially fatal infections in whom the diagnosis is firmly established.[4]

While some azole antifungal agents (e.g., itraconazole, fluconazole) are now also recognized as drugs of choice for the treatment of many systemic mycoses, amphotericin B deoxycholate remains the drug of first choice for the initial treatment of severe, life-threatening fungal infections, especially in immunocompromised patients. Because clinical experience with newer amphotericin B formulations is limited, these formulations have generally been reserved for second-line therapy in patients with invasive fungal infections that have not responded to amphotericin B deoxycholate or in patients who cannot tolerate amphotericin B deoxycholate.[5] Specific indications are listed below by formulation.

Amphotericin B cholestryl sulfate complex is indicated for the treatment of invasive aspergillosis in cases where renal impairment or unacceptable toxicity precludes the use of amphotericin B deoxycholate in effective doses and in cases where prior amphotericin B deoxycholate therapy has failed.[6]

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Non-HIV/AIDS-Related Uses (cont.)

Amphotericin B lipid complex is indicated for the treatment of invasive fungal infections in patients who are refractory to or intolerant of amphotericin B deoxycholate therapy.[7]

Amphotericin B liposomal is indicated as empiric therapy for presumed fungal infections in febrile, neutropenic patients; treatment of cryptococcal meningitis in HIV infected patients; treatment of aspergillosis, candidiasis, or cryptococcosis in patients refractory to amphotericin B deoxycholate or with renal impairment that precludes the use of amphotericin B deoxycholate; and the treatment of leishmaniasis.[8]

Amphotericin B deoxycholate may be the preferred agent for pregnant women with invasive fungal infections due to concerns regarding the use of azole antifungal agents during pregnancy. Intravenous amphotericin B has also been used for empiric therapy in febrile neutropenic patients and for prophylaxis in certain immunosuppressed individuals (e.g., cancer patients and bone marrow or solid organ transplant patients).[9]

Amphotericin B is also used for the treatment of certain protozoal infections, including leishmaniasis and amebic meningoencephalitis. Amphotericin B is not effective against bacteria, rickettsiae, or viruses.[10]

Pharmacology

Amphotericin B is fungistatic or fungicidal, depending upon the susceptibility of the fungus and the concentration obtained in body fluids. Amphotericin binds to sterols in the fungal cell membrane, changing the membrane permeability and causing leakage of intracellular components.[11] Cell death occurs in part because of these permeability changes, but other mechanisms may also contribute to amphotericin's antifungal activity. Amphotericin B is not active in vitro against organisms that do not contain sterols in their cell membranes (e.g., bacteria). Binding to sterols in mammalian cells (such as certain kidney cells and erythrocytes) may be responsible for the toxicities associated with amphotericin B therapy.[12]

Amphotericin B is poorly absorbed from the gastrointestinal (GI) tract and must be given parenterally to treat systemic fungal infections.[13] Peak plasma concentrations of about 0.5 to 2 mcg/ml result from repeated intravenous (IV) amphotericin B doses of approximately 0.5 mg per kg per day.[14]

Amphotericin B distributes into lungs, liver, spleen, kidneys, adrenal glands, muscle, and other tissues in potentially therapeutic concentrations. The volume of distribution is approximately 4 l/kg in adults. Concentrations attained in pleural, peritoneal, and synovial fluids and in aqueous humor are reportedly about two-thirds the concentration in plasma.[15] Concentrations in cerebrospinal fluid (CSF) are approximately 3% of concurrent serum concentrations. To achieve fungistatic CSF concentrations, amphotericin B must be administered intrathecally.[16]

Amphotericin B reportedly crosses the placenta, and low concentrations are attained in amniotic fluid. Amphotericin B is in FDA Pregnancy Category C. Safe use of amphotericin B during pregnancy has not been established. Animal studies have not revealed evidence of harm to the fetus. It is not known if amphotericin B is distributed into breast milk.[17] [18]

Amphotericin B is highly protein bound (greater than 90 percent). Metabolism of amphotericin B has not been fully elucidated. The initial plasma elimination half-life is 24 hours and the terminal elimination half-life is approximately 15 days. Amphotericin B is eliminated very slowly (weeks to months) by the kidneys; only about 40% of an administered dose is excreted over 7 days. Only 3% of a dose is excreted in the urine unchanged. Amphotericin B is not hemodialyzable.[19]

Resistance to amphotericin B has been produced in vitro, and resistant strains have been isolated from patients who have received long-term therapy with amphotericin B deoxycholate. Fluconazole-resistant strains of Candida albicans that were cross-resistant to amphotericin B have been isolated from a few immunocompromised patients. Cryptococcus neoformans isolates resistant to fluconazole and amphotericin B have also been documented. Fungi resistant to amphotericin B deoxycholate may also

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Pharmacology (cont.)

be resistant to amphotericin B cholestryl sulfate complex, amphotericin B lipid complex, and amphotericin B liposomal.[20]

Adverse Events/Toxicity

Most patients on amphotericin B deoxycholate therapy experience adverse effects. Acute infusion reactions and nephrotoxicity are the two most common adverse effects.

The majority of patients receiving amphotericin B deoxycholate (50% to 90%) experience some degree of intolerance to initial doses. Acute infusion reactions of fever, shaking chills, hypotension, anorexia, nausea, vomiting, headache, dyspnea, and tachypnea may occur 1 to 3 hours after initiation of IV infusions. Lipid-based amphotericin B preparations are also associated with acute infusion reactions, although to a lesser degree. Administration of an antipyretic, an antihistamine, meperidine, and/or a corticosteroid just before the start of the infusion may reduce the incidence or severity of the reaction.

Rapid infusion of amphotericin B deoxycholate has been associated with a more severe reaction consisting of hypotension, bronchospasm, hypokalemia, arrhythmias, and shock. It may be difficult to determine whether these severe reactions indicate intolerance or hypersensitivity to amphotericin B. Anaphylaxis and anaphylactoid reactions have been reported in people taking all formulations of amphotericin B.

Nephrotoxicity is the major dose-limiting toxicity reported with amphotericin B deoxycholate, and nephrotoxicity occurs to some degree in the majority of patients receiving the drug. Adverse renal effects include decreased renal function, azotemia, hypokalemia, hyposthenuria, renal tubular acidosis, and nephrocalcinosis. Increased BUN and serum creatinine concentrations and decreased creatinine clearance, glomerular filtration rate, and renal plasma flow occur in most patients. Nephrotoxicity associated with amphotericin B deoxycholate appears to involve several mechanisms, including direct vasoconstrictive effects on renal arterioles and lytic action on renal tubular cell membranes. Renal function usually improves within a few months of discontinuing therapy, but some impairment may remain. Lipid-based amphotericin B formulations are generally associated with a lower risk of nephrotoxicity than amphotericin B deoxycholate. However, abnormal renal lab values have been reported in patients using alternate formulations.[21]

Amphotericin B intravenous infusion has also been associated with anemia, headache, thrombophlebitis, and GI effects (indigestion, loss of appetite, nausea, vomiting, diarrhea, stomach pain). Less frequently, blurred or double vision, cardiac arrhythmias, leukopenia, polyneuropathy, seizures, and thrombocytopenia have been reported.[22]

Drug and Food Interactions

Since nephrotoxic effects may be additive, the concurrent or sequential use of amphotericin B and other drugs with similar nephrotoxic effects (e.g., aminoglycosides, vancomycin, cyclosporine, and pentamidine) should be avoided. Intensive monitoring is recommended in patients requiring concomitant administration of any nephrotoxic medications.[23]

Concomitant administration of zidovudine and amphotericin B may be associated with increased myelotoxicity and nephrotoxicity.[24]

Concomitant administration of flucytosine and amphotericin B may have additive or slightly synergistic effects. Amphotericin B-induced renal dysfunction may decrease the clearance of flucytosine, resulting in flucytosine adverse effects such as bone marrow toxicity.

Amphotericin B coadministered with blood dyscrasia-causing medications, bone marrow depressants, or radiation therapy may increase the chance of anemia or other hematologic effects. Dosage reduction may be required.

When administered concurrently, corticosteroids, corticotropin (ACTH), or potassium-depleting diuretics may potentiate amphotericin B-induced hypokalemia. Amphotericin B-induced

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Drug and Food Interactions (cont.)

hypokalemia may potentiate digitalis toxicity.[25]

Contraindications

Amphotericin B deoxycholate and alternative formulations of amphotericin B are contraindicated in patients allergic to amphotericin B or any of the formulation components. Extreme caution should be exercised when using amphotericin B deoxycholate in patients with renal impairment.[26]

Clinical Trials

For information on clinical trials that involve Amphotericin B, visit the ClinicalTrials.gov web site at http://www.clinicaltrials.gov. In the Search box, enter: Amphotericin B AND HIV Infections.

Dosing Information

Mode of Delivery: Intravenous infusion. May also be given intrathecally, intra-articularly, intrapleurally, and by local instillation or irrigation.[27]

Dosage Form: Powder for injection (50 mg vials).[28]

Storage: Prior to reconstitution, store powder between 2 C and 8 C (36 F and 46 F). Protect from light.[29]

Chemistry

CAS Name: (1R-(1R*,3S*,5R*,6R*,9R*,11R*, 15S*,16R*,17R*,18S*,19E,21E,23E,25E,27E,29E, 31E,33R*,35S*,36R*,37S*))-33-((3-Amino-3,6-dideoxy-beta-D-mannopyranosyl)oxy)-1,3,5,6,9, 11,17,37-octahydroxy-15,16,18-trimethyl-13-oxo-14,39-dioxabicyclo(33.3.1)nonatriaconta-19,21, 23,25,27,29,31-heptaene-36-carboxylic acid[30]

CAS Number: 1397-89-3[31]

Molecular formula: C47-H73-N-O17[32]

C61.09%, H7.96%, N1.52%, O29.43%[33]

Molecular weight: 924.08[34]

Physical Description: Yellow to orange, odorless or practically odorless powder.[35]

Stability: Concentrated solutions (5 mg/ml) in sterile water retain their potency for 24 hours at room temperature if protected from light, or for 1 week if refrigerated. Diluted solutions (0.1 mg/ml) in 5% dextrose should be used promptly after dilution.[36]

Solubility: Crystalline amphotericin B is insoluble in water. It is solubilized by the addition of sodium deoxycholate to form a mixture, which creates a colloidal dispersion.[37]

Other Names

Amphotericin B cholestryl complex[38]

Amphotericin B lipid complex[39]

Amphotericin B liposomal complex[40]

Mysteclin-F[41]

Liposomal Amphotericin B[42]

Further Reading

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Manufacturer Information

Amphotericin B
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

Fungizone
Bristol - Myers Squibb Co
PO Box 4500
Princeton, NJ 08543-4500
(800) 321-1335

Amphocin
Pfizer Inc
235 East 42nd Street
New York, NY 10017-5755
(800) 438-1985

AmBisome
Fujisawa Healthcare Inc
Parkway Center North / 3 Parkway North
Deerfield, IL 60015-2548
(800) 727-7003

Abelecet
Enzon, Inc.
20 Kingsbridge Road
Piscataway, NJ 08854-3969
(908) 541-8600

Amphotec
Oryx Pharmaceuticals Inc.
6500 Kitimat Road
Mississauga, Ontario, Canada

For More Information

Contact your doctor or an AIDSinfo Health Information Specialist:

• Via Phone: 1-800-448-0440 Monday - Friday, 12:00 p.m. (Noon) - 5:00 p.m. ET

• Via Live Help: http://aidsinfo.nih.gov/live_help Monday - Friday, 12:00 p.m. (Noon) - 4:00 p.m. ET

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